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Decision Making in Critical Limb Ischemia: A Markov Simulation

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Abstract

Background—Critical limb ischemia (CLI) is a feared complication of peripheral vascular disease that often requires surgical management and may require amputation of the affected limb.

Objective—To use a decision model to inform clinical management for a 63-year-old woman with CLI and multiple medical comorbidities, including advanced heart failure and diabetes.

Methods—Markov decision model evaluating four strategies: amputation, surgical bypass, endovascular therapy (e.g. stent or revascularization), and medical management. We measured the impact of parameter uncertainty using 1-way, 2-way, and multi-way sensitivity analyses.

Results—In the base case, endovascular therapy yielded similar discounted quality-adjusted life-months (26.50 QALMs) compared to surgical bypass (26.34 QALMs). Both endovascular and surgical therapies were superior to amputation (18.83 QALMs), and medical management (11.08 QALMs). This finding was robust to a wide range of peri-procedural mortality weights, and was most sensitive to long-term mortality associated with endovascular and surgical therapies.

Limitations—Utility weights were not stratified by patient comorbidities; nonetheless, our conclusion was robust to a range of utility weight values.

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Conclusions—For a patient with CLI, endovascular therapy and surgical bypass provided comparable clinical outcomes. However, this finding was sensitive to long-term mortality rates associated with each procedure. Both endovascular and surgical therapies were superior to amputation or medical management in a range of scenarios.

Keywords

critical limb ischemia; surgical bypass; endovascular therapy; decision analysis; Markov model

1. INTRODUCTION¹

Ms. F was a woman in her early sixties who presented to an academic medical center with a foul-smelling foot. She had a history of insulin-dependent diabetes with multiple complications, including severe retinopathy and peripheral neuropathy. She had coronary artery disease with prior myocardial infarctions, ischemic cardiomyopathy with reduced ejection fraction, and prior ischemic cerebrovascular accidents. She had undergone right transmetatarsal amputation a few years prior for peripheral arterial disease.

On presentation, she reported that the first and second digits on her left foot had “turned black.” She also had progressive loss of sensation of the involved foot, and she had become more sedentary due to decreased mobility. She did not seek medical attention because she feared amputation. Review of systems was notable for occasional chills, but no fevers. She additionally had intermittent chest pain that occurred at rest with no clear pattern of onset, although she reported this pain was relieved with full-strength aspirin.

Ms. F lived in a two-story home with her extended family. She was the primary caretaker for three children during working hours. For multiple reasons, including her limited eyesight, poor social support, and concerns about adverse reactions to certain medications, she had not taken her prescribed medications. Indeed, she had not seen a physician for about 18 months.

On physical examination, Ms. F was afebrile with normal vital signs. She appeared chronically ill, lying in bed. Examination of her left lower extremity revealed necrotic first and second digits, with warmth and erythema extending to just above the medial malleolus. There was no purulence noted. Laboratory evaluation revealed a white blood cell count of 18,900/mm³ with 88% neutrophils, an erythrocyte sedimentation rate of 122 mm/hr, C-reactive protein of 147 mg/L, and hemoglobin A1c of 12%.

Ms. F received broad-spectrum intravenous antibiotics. Vascular surgery was consulted and they performed a debridement and amputation of the first three toes on hospital day (HD) #5. With these interventions, her foot erythema improved. However, over the next two weeks she continued to have necrosis of distal tissues, suggesting ongoing vascular insufficiency. Therefore, alternative management plans were considered given inconclusive guidelines for a patient like Ms. F [1,2].

¹Abbreviations: CLI, critical limb ischemia; HD, hospital day; QALM, quality-adjusted life-month; QALY, quality-adjusted life-year

Ms. F's hospital course was complicated by acute kidney injury, recurrent angina at rest, poor nutritional status, and situational depression that resulted in limited engagement about her health. She expressed her strong desire to go home as soon as possible for family reasons.

Together with the vascular surgeons, the patient, the patient's family, and the medical team evaluated four possible strategies: (1) Below-the-knee amputation, (2) Surgical bypass, (3) Endovascular therapy, and (4) Medical management. Given the complexity and gravity of the decision, the medical team developed a decision analysis model to help guide management [3]. While the original decision tree was sketched on the white board during clinical work rounds with parameter estimates, subsequent literature and model refinement occurred throughout Ms. F's hospitalization and after her discharge.

2. MATERIALS AND METHODS

2.1 Analytic Overview

We constructed a Markov decision analysis model to evaluate four treatment strategies for Ms. F, a patient with CLI. We considered:

1. Below-the-knee amputation,
2. Surgical bypass,
3. Endovascular therapy (e.g. stent or revascularization), or
4. Medical management.

We considered Ms. F's options at the time of presentation. We assigned monthly probabilities of disease progression and death over a 25-year time horizon. The primary model outcome was quality-adjusted life-months (QALMs), and we used the model to assess which strategy yielded the highest total QALMs in the base case. We then modified key parameters to conduct one-way, two-way, and multi-way sensitivity analyses.

2.2 Model Structure and Strategies

The decision tree (TreeAge Pro 2014, TreeAge Software, Inc., Williamstown, MA) included a choice of four initial therapies (Figure 1, Figure A.1). Within each branch, the therapy could succeed or fail, and the patient could live or die. At the end of a patient's course through the decision tree (at the rightmost side of the figure), the probabilities were multiplied by a health utility weight ranging from 0 to 1, where 0 represented death and 1 represented perfect health. If the patient died, the model stopped. If the patient was still alive, then the model returned to a previous node, as designated in the figure. Cumulative quality-adjusted life-months were calculated for each path through the tree. We applied an annual discount rate of 3% to the quality-adjusted life-months and reported outcomes with and without discounting [4].

For two of the initial options (endovascular therapy and surgical bypass), we introduced the possibility of therapeutic failure (e.g. stent or bypass occlusion). In these cases, the patient could choose to repeat the initial procedure or to undergo one of the remaining three

therapies, which were constructed as “clones” of the initial branch on the tree diagram. We assumed each patient would undergo each procedure a maximum of two times [5]. Additionally, we assumed that patients who initially chose medical management would not later opt for a surgical procedure.

2.3 Input Parameters

We obtained mortality rates, operative failure rates, and quality of life estimates associated with each strategy from literature estimates (Table I) [6–12]. All rates were expressed as rates over one-month intervals.

2.4 Sensitivity and Additional Analyses

We varied each parameter using ranges from the published literature (Table I, rightmost column). In certain cases, trial outcomes were reported as a proportion, $\hat{p}$, of individuals from a sample size of n participants, but confidence intervals were not included; in these cases, we calculated a 95% confidence interval assuming a mean of $\hat{p}$ and a standard error of

$$SE(\hat{p}) = \sqrt{\frac{\hat{p}(1-\hat{p})}{n}}.$$

For the most influential of these individual parameters, we varied these inputs simultaneously in two- and multi-way sensitivity analyses.

In addition, we constructed a separate decision model to determine how to proceed after Ms. F underwent a failed endovascular procedure, a critical juncture in her care during her hospitalization (Figure A.2). This model had a parallel structure to the more extensive tree in the primary analysis, with changes in the location of Markov and decision nodes reflecting this patient’s specific clinical course.

3. RESULTS

3.1 Base Case

In the base case, measuring undiscounted quality-adjusted life-months (QALMs), endovascular therapy provided the maximal clinical benefit with 29.15 QALMs (2.43 quality-adjusted life-years (QALYs)) (Table II). This strategy was closely followed by surgical bypass, with 28.90 QALMs (2.41 QALYs), a difference of 0.25 QALMs. Both strategies were superior to amputation (20.62 QALMs = 1.72 QALYs) and medical management (11.82 QALMs = 0.99 QALYs). After applying a 3% annual discount, endovascular therapy remained the optimal strategy with 26.50 QALMs, and was followed closely by surgical bypass (26.34 QALMs), a difference of 0.16 QALMs. Both strategies were superior to amputation (18.83 QALMs) and medical management (11.08 QALMs), a difference of 7.67 QALMs and 15.42 QALMs, respectively, compared to endovascular therapy.

3.2 One-Way Sensitivity Analyses

In the absence of utility weights, endovascular therapy yielded greater life expectancy compared to surgical bypass (38.94 months versus 38.22 months), and the overall life expectancy for amputation (34.83 months) was similar to that for endovascular or surgical therapy (Table II). Without utility weights, medical management continued to have the shortest life expectancy (25.92 months).

The finding that endovascular therapy was superior to surgical bypass was robust to a range of input parameters, and it was most sensitive to long-term (non-perioperative) mortality due to endovascular or surgical therapy (Figure 2). If the monthly mortality associated with endovascular therapy was greater than 2.1%, or the mortality associated with surgical bypass was less than 2.4%, then surgical bypass became the best option (Figure 2).

3.3 Two- and Multi-Way Sensitivity Analyses

In two-way sensitivity analyses, we varied long-term mortality rates for endovascular therapy, surgical bypass, and medical management. We found that medical management could be the optimal strategy in certain cases. For example, if the monthly mortality associated with medical management was less than 1.4% and the mortality due to surgical bypass was greater than 2.4%, then medical management became the optimal strategy (Figure 3). Over a range of plausible parameters for perioperative and long-term mortality rates, we found that endovascular therapy and surgical bypass were comparable, and both were superior to amputation and medical management (Figure 3).

3.4 Patient-Specific Results

In the patient-specific tree designed to model Ms. F's options after she underwent a failed endovascular procedure, we found that repeat endovascular procedure was the optimal strategy, yielding 25.93 QALMs. This strategy was superior to surgical bypass (24.20 QALMs), amputation (17.87 QALMs), and medical management (10.79 QALMs). This is in fact the treatment that Ms. F received. However, as detailed in the Case Outcome section below, the repeat endovascular procedure also failed and she ultimately received an amputation.

4. DISCUSSION

We used decision analysis to inform the care of a complex patient presenting with CLI by evaluating four options: amputation, surgical bypass, endovascular therapy, and medical management. We found that endovascular therapy was comparable to surgical bypass in the base case, providing 0.16 quality-adjusted life-months over the next best strategy, surgical bypass (26.50 versus 26.34 QALMs). These findings are comparable to the small gains (approximately 0.01–1.2 QALMs) found in recent studies when comparing differing endovascular therapy modalities [13,14]. Similar to this analysis, the 2005 Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial found that endovascular therapy and surgical bypass had similar quality of life at 3 years after randomization, and there was no significant mortality difference between the two strategies [8,15,16]. However, while the BASIL trial compared surgical bypass to standard angioplasty, there are no randomized data

comparing surgical bypass to more recent advanced endovascular interventions (such as atherectomy, drug-eluting stents, drug-coated balloons, woven nitinol stenting or transpedal access) [1,17].

Our findings build on the analysis by Hunink and colleagues, who compared endovascular therapy and surgical bypass using a Markov model and literature-based estimates [5]. Compared to the findings by Hunink and colleagues, we found a smaller difference in QALMs between endovascular therapy and surgical bypass. However, our analysis demonstrated that both endovascular and surgical therapies offer substantial (7.67–15.42 QALMs) gains over amputation and medical management for CLI, and these benefits were larger than those found by Hunink and colleagues. While our analysis combines more recent literature reflecting advances in endovascular techniques, the analysis by Hunink and colleagues additionally stratified outcomes by symptoms and vessel occlusion. The more substantial differences found by Hunink and colleagues between therapies when stratifying symptoms and vessel occlusion highlights a need for more robust, updated, and detailed outcomes data for CLI, a need also highlighted by the Vascular Quality Initiative and the AHA/ACC recommendations [1,18]. Ongoing trials, such as the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia trial (BEST-CLI; ClinicalTrials.gov: NCT02060630) and BASIL-2 will provide additional information, particularly in light of more recent advanced interventions in endovascular therapies [19–21].

We found that determination of the optimal strategy in CLI was most sensitive to changes in post-procedural long-term mortality. The effect of higher perioperative mortality from surgical bypass is most easily appreciated in the one- and two-way sensitivity analyses (Figures 2 and 3, particularly 3D). While the one-way sensitivity analysis showed a narrow benefit to endovascular therapy overall (Figure 2), the two-way sensitivity analysis demonstrated benefits to endovascular therapy for mortality and health utility regardless of the initial management strategy choice (Figure 3). Thus, this analysis suggests that care providers must strongly consider the overall life expectancy for patients with multiple comorbidities and higher perioperative mortality, such as our patient [22–24]. Many decisions in CLI will continue to require personalization.

In our patient's specific scenario, in which Ms. F had already undergone one endovascular procedure, we identified that repeat endovascular procedure maximized clinical outcomes compared to surgical bypass by 1.73 QALMs (25.93 versus 24.20 QALMs). In both models, the slight superiority of endovascular therapy reflected the benefits of the low mortality risk of endovascular therapies compared to surgical bypass (Figure 3D). The difference between endovascular therapy and surgical bypass was larger for the patient-specific scenario compared to the primary model (1.73 versus 0.16 QALMs) because if endovascular therapy was chosen first, the patient had more opportunities to undergo a low mortality procedure (i.e. repeat endovascular therapy once and subsequently bypass twice), thereby avoiding the higher mortality associated with amputation or medical management. If the patient instead chose bypass first, she could only undergo repeat bypass once and could not subsequently undergo endovascular therapy, and she thus had fewer opportunities to avoid the higher mortality associated with amputation or medical management. The greater value of

endovascular therapy compared to surgical bypass in this second, patient-specific tree highlights the usefulness of patient-specific models to inform clinical care [13]. Of note, popular surgical risk calculators, such as the Universal Risk Calculator published by the American College of Surgeons [25], do not specify different perioperative risks between endovascular and surgical revascularization, further supporting the value of patient-specific models.

This model-based analysis of CLI has several limitations. Model inputs were derived primarily from retrospective cohort data. These data did not consistently stratify outcomes by patient comorbidities; however, we used the highest-quality data available, and we varied all input parameters over plausible ranges and reported conclusions that were robust to a wide range of clinical scenarios. Additionally, our patient had considerable underlying medical comorbidities that made her somewhat distinct from many patients included in the randomized controlled trial and among the sicker patients included in the observational studies, which limited our ability to accurately apply our findings to Ms. F.

5. CASE OUTCOME AND CONCLUSIONS

Vascular surgery performed an initial unsuccessful endovascular procedure and recommended repeat endovascular management of Ms. F's foot, as was projected to be optimal in the patient-specific model. On HD#19, Ms. F underwent a repeat angiogram, with successful angioplasty. However, despite appropriate blood flow visualized on post-angioplasty angiography, Ms. F continued to have poor distal perfusion during her hospitalization. Below-the-knee amputation on HD#29 was subsequently performed without complications, and she was discharged to a physical rehabilitation facility on HD#34.

This decision analysis for CLI projected that endovascular therapy and surgical bypass provided comparable clinical outcomes. Both endovascular and surgical therapy were superior to amputation or medical management in a range of scenarios. Decision analytics can be a powerful bedside tool to help shared decision making in CLI. However, more comprehensive data with standardized outcomes and a user-friendly bedside tool are needed to reliably and readily apply decision analysis methods to guide multidisciplinary teams with patients in real-time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. State Transition Diagrams

These diagrams display the possible transitions between health states in each of the four branches of the Markov decision analysis model: **(A)** Amputation, **(B)** Surgical bypass, **(C)** Endovascular therapy, and **(D)** Medical management. Nodes represent health states, while arrows represent possible transitions between these health states. Each Markov model starts at the node marked “1” and ends when the patient reaches the “Dead” state, or after 25 years have elapsed. The monthly probability of transitioning to a certain health state is given in Table I. For surgical bypass and endovascular therapy, we assumed each procedure could be repeated exactly once (*i.e.* a maximum of two total procedures).

Figure 2. One-Way Sensitivity Analysis

The tornado diagram displays the number of quality-adjusted life-months resulting from surgical bypass (dark gray bars) or endovascular therapy (light gray bars), after varying operative mortality and failure rates over the ranges listed on the vertical axis. Each horizontal bar represents the range of expected values generated by varying the indicated parameter across its plausible range. The vertical dashed lines represent the expected outcome in the base case. The model is sensitive to a given parameter if the horizontal bars overlap for that parameter, indicating that the optimal strategy depends on precise value of the input variable.

Figure 3. Two-Way Sensitivity Analyses

In these graphs, selected pairs of input parameters are varied simultaneously. The optimal strategy (surgical bypass, endovascular therapy, or medical management) is displayed in each shaded region. Dashed lines represent the base case value of each input parameter. **(A)** Long-term mortality after surgical bypass vs. long-term mortality after endovascular therapy. **(B)** Long-term mortality after surgical bypass vs. long-term mortality after medical management. **(C)** Long-term mortality after endovascular therapy vs. long-term mortality after medical management. **(D)** 30-day perioperative mortality after surgical bypass vs. 30-day perioperative mortality after endovascular therapy.

Table I**Input Parameters for a Decision Analysis Model of CLI**

	Value	Range for Sensitivity Analysis
Probability of perioperative mortality[*]		
Amputation [6,7]	10%	7–22%
Surgical bypass [8]	5.58%	2.38–8.79%
Endovascular therapy [8]	2.95%	0.80–5.11%
Probability of long-term mortality[†]		
Amputation [9]	2.55%	2.01–3.13%
Surgical bypass [8]	2.41%	1.59–3.26%
Endovascular therapy [8]	2.04%	1.28–2.83%
Medical management [6,10]	3.65%	1–5%
Probability of non-healed operative site[*]		
Amputation [6]	15%	
Monthly probability of vascular occlusion[‡]		
Surgical bypass		
0–1 month [11]	6.70%	
1–6 months [11]	1.66%	
6–12 months [11]	0.85%	
12–24 months [11]	0.50%	
> 36 months [11]	0.50%	
Endovascular therapy		
0–1 month [11]	22.6%	
1–6 months [11]	3.43%	
6–12 months [11]	1.85%	
12–24 months [11]	1.03%	
> 36 months [11]	0.45%	
Proportion of patients choosing each secondary procedure		
Initial procedure: surgical bypass[§]		
Amputation [8]	0.357	
Surgical bypass (repeat) [8]	0.179	
Endovascular therapy [8]	0.411	
Medical management [8]	0.054	
Initial procedure: endovascular therapy[§]		
Amputation [8]	0.182	
Surgical bypass [8]	0.523	
Endovascular therapy (repeat) [8]	0.148	
Medical management [8]	0.148	
Health utility weights according to outcome [12]		

	Value	Range for Sensitivity Analysis
Initial procedure: amputation		
Healed	0.636	
Non-healed	0.372	
Initial procedure: surgical bypass		
Patent after first operation	0.816	
Patent after repeat operation	0.756	
Non-patent, requires amputation	0.552	
Non-patent, managed medically	0.396	
Initial procedure: endovascular therapy		
Patent after first operation	0.864	
Patent after repeat operation	0.852	
Non-patent, requires amputation	0.600	
Non-patent, managed medically	0.444	
Initial procedure: medical management		
Rest pain and gangrene	0.456	

* Probability of event occurrence in the first 30 days following the procedure.

[†] Probability of event occurrence per month after the first 30 days. To obtain monthly probabilities, we calculated the monthly rate (r) using the formula $r = -\ln(1 - p)/t$, where p is the probability of death over time t . Then, we calculated the updated probability (p') using the formula $p' = 1 - e^{-rt'}$ and setting t' equal to 1 month.

[‡] Probability of event occurrence per month during the indicated number of months following the procedure.

[§] Proportions do not add to 1 due to rounding.

Table II

Base Case Results

Decision	Life Expectancy (Months)	Quality-Adjusted Life Expectancy (Quality-Adjusted Life-Months [QALMs])	
	Undiscounted	Undiscounted	Discounted*
Amputation	34.83	20.62	18.83
Surgical bypass	38.22	28.90	26.34
Endovascular therapy	38.94	29.15	26.50
Medical management	25.92	11.82	11.08

* Using an annual discount rate of 3% [4]